Ticagrelor Improves Peripheral Arterial Function in Acute Coronary Syndrome Patients

Relationship With Adenosine Plasma Level

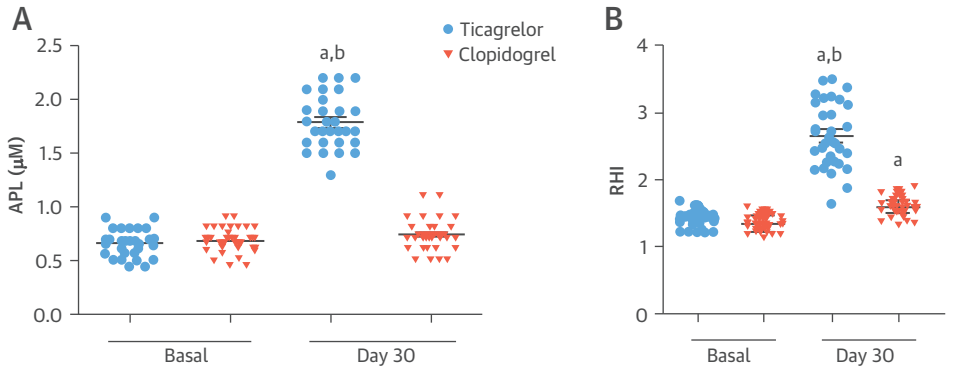
Ticagrelor, a $P2Y_{12}$ receptor antagonist, significantly reduces the incidence of major cardiovascular events in acute coronary syndrome (ACS) compared with standard treatment with clopidogrel (1). It has been suggested that this benefit effect may be accounted for by its pleiotropic properties via a purinergic mechanism. Indeed, ticagrelor increases the endogenous adenosine plasma level (APL) via red blood cell uptake inhibition in primary ACS patients compared with clopidogrel (2). However, the link between these "pleiotropic" properties and the improvement in microvascular dysfunction (MiD) remains poorly investigated. This study aimed to determine whether the increase in APL achieved with ticagrelor might improve endothelial dysfunction in primary ACS patients.

We prospectively randomized 60 primary ACS patients to receive ticagrelor (180-mg loading dose followed by 90 mg twice daily) or clopidogrel (600-mg loading dose followed by 75 mg/day). In addition, all patients received 250 mg of ticagrelor followed by 75 mg of aspirin daily. Exclusion criteria were New York Heart Association functional class III or higher, cardiac arrest, contraindications to antiplatelet therapy, treatment with a $P2Y_{12}$-adenosine diphosphate receptor antagonist for <1 month, a platelet count <100 g/l, a history of bleeding diathesis, a history of stroke, recent surgery (preceding month), use of a medication known to interfere with ticagrelor, and bradycardia. Blood samples (3 ml) were collected under basal conditions (just before the primary loading dose) and after 30 days of treatment. APL was measured as previously described using high-pressure liquid chromatography (2).

To assess MiD, we performed digital peripheral artery tonometry at the same time to evaluate the reactive hyperemia index (RHI). Endothelial dysfunction was suspected if the RHI was <1.67. The methodology has been previously described (3). Briefly, each recording consisted of 5 min of baseline measurements, 5 min of occlusion measurements, and then 5 min of post-occlusion measurements (hyperemic period) (3). The RHI was defined as the ratio of the digital pulse volume during reactive hyperemia to that observed at baseline. Adverse cardiovascular events were recorded.

Under basal conditions, all the patients had MiD (RHI <1.67; mean, 1.37 ± 0.12). The APL (**Figure 1A**) and RHI (**Figure 1B**) did not differ between the 2 groups of patients. At day 30, the APL increased significantly only in the ticagrelor group (**Figure 1A**). The APL was more than 2-fold higher in patients taking ticagrelor

FIGURE 1 APL and RHI 30 Days After Treatment



Continuous variables were expressed as mean ± SD or median and interquartile range. The Wilcoxon test was used for intraindividual comparisons. Analysis of variance was used for intergroup comparisons. Pearson's *r* coefficient of correlation was used for a correlation study. APL **(A)** or RHI **(B)** was measured before (basal) and after 30 days of treatment. Correlation between the mean APL was evaluated after 30 days of ticagrelor treatment, the mean APL was evaluated before treatment (ΔAPL), and the RIH was evaluated after 30 days of ticagrelor treatment. The RHI was evaluated under basal conditions (ΔRHI). **(a)** $p < 0.01$ compared with basal conditions. **(b)** $p < 0.01$ compared with the clopidogrel group. APL = adenosine plasma level; RHI = reactive hyperemia index.

than in patients taking clopidogrel (Figure 1A). After 30 days, the mean RHI increased slightly (mean, +15%) in the clopidogrel group and greatly (+100%) in the ticagrelor group (Figure 1B). We found a correlation between the increase in the APL and the increase in the RHI in the ticagrelor group. No ischemic or bleeding events were recorded within 1 month. Dyspnea was present in 7 patients in the ticagrelor group and in 5 patients in the clopidogrel group.

Treatment with ticagrelor improves peripheral arterial function compared with clopidogrel. Endothelial function responds quickly to ticagrelor therapy within 30 days, long before the effects on clinical outcomes are seen. The underlying mechanism seems to be the APL increase. It was shown that clopidogrel slightly improved endothelial function (4); however, we found that these effects were not related to an increase in adenosine plasma concentration. It was shown that the ticagrelor dose dependently increased adenosine-mediated coronary blood flow in healthy human subjects (5). These effects occur mostly via the activation of A_{2A} adenosine receptors. Here, we found that ticagrelor induces an increase in the APL that correlates with the increase in the RHI. Because a low RHI is associated with a higher adverse rate during follow-up, our study led to the hypothesis that the adenosine-mediated effects of ticagrelor may explain the accuracy of the PLATO (A Comparison of Ticagrelor (AZD6140) and Clopidogrel in Patients With Acute Coronary Syndrome) mortality data (1).

Finally, our study demonstrates a correlation between the increase in the APL and improvement in the RHI, but whether this increase in the APL has a direct effect on endothelial function remains to be established.

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http://dx.doi.org/10.1016/j.jacc.2016.02.023

Please note: Dr. Bonello has received a research grant from AstraZeneca. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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Is it Time for a New Paradigm in Asymptomatic Severe Aortic Stenosis?

We read with interest the paper by Taniguchi et al. (1), who reported that a strategy of earlier aortic valve replacement (AVR) in patients with asymptomatic severe aortic stenosis (AS) was associated with a lower long-term risk of hospitalization for heart failure or all-cause mortality compared with the strategy currently recommended in clinical practice guidelines, which is to wait for the onset of symptoms before intervention.

Two important issues should be considered regarding the clinical relevance of this study. First, Taniguchi et al. (1), in the collection of baseline clinical information, reported the classic symptoms of angina, syncope, or heart failure as AS-related symptoms. These symptoms are typically the later manifestation of disease and now are seen only in patients who do not receive medical care, fail to report early symptoms, or have an inappropriate surgical delay (2). Second, although the study methods were robust, asymptomatic status was not confirmed by a treadmill exercise test; therefore, it was possible that some symptoms were undetected or unrecognized in some patients due to a sedentary life-style. Among patients with asymptomatic severe AS, cardiopulmonary exercise testing (CPET) provides more sensitive detection of exercise intolerance than the stress test criteria recommended in the guidelines (3).